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Mini-review

Chemopreventive and therapeutic effects of curcumin

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Abstract

Chemoprevention is a promising anti-cancer approach with reduced secondary effects in comparison to classical chemotherapy. Curcumin, one of the most studied chemopreventive agents, is a natural compound extracted from *Curcuma longa L.* that allows suppression, retardation or inversion of carcinogenesis. Curcumin is also described as an anti-tumoral, anti-oxidant and anti-inflammatory agent capable of inducing apoptosis in numerous cellular systems. In this review, we describe both properties and mode of action of curcumin on carcinogenesis, gene expression mechanisms and drug metabolism.

Keywords: Chemopreventive agent; Curcumin; Cancer; Apoptosis; Drug metabolism

1. Introduction

Chemoprevention was described as the use of natural or synthetic chemicals allowing suppression, retardation or inversion of carcinogenesis [1]. Chemopreventive products present low side effects and toxicity, neutralisation of carcinogens as well as their effects on cells.

Most chemopreventive agents known until today are plant extracts subdivided into two classes: (i) blocking agents, which inhibit the initiation step by preventing carcinogen activation and (ii) suppressing agents, which inhibit malignant cell proliferation during promotion and progression steps of carcinogenesis (Fig. 1).

Agents, such as kahweol and cafesteol (Fig. 2), two diterpens present in coffee, possess a strong chemopreventive potential and were shown to protect cells against mutagenesis and carcinogenesis in animal models [2]. Similar effects were observed with compounds from garlic like diallyl sulphide (Fig. 2), which blocks carcinogenesis in mice, presumably due to essential allyl groups and a central disulphuric chain.

Cassia siamea compound emodin (Fig. 2) presents strong anti-tumoral effects on 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA)-induced skin tumour in mice [3] and lycopene, extracted from tomatoes, blocks dimethyl benzanthracene (DMBA)-induced carcinomas in hamster [4].

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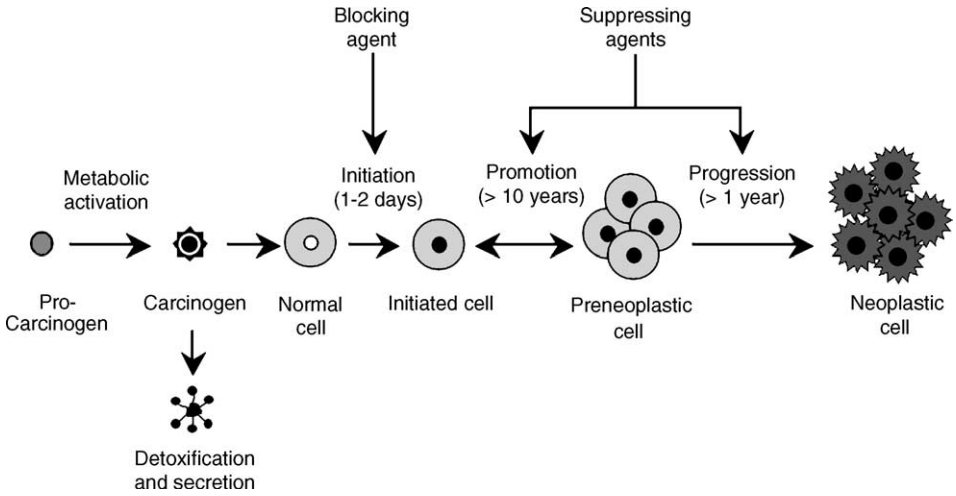

Fig. 1. Schematic representation of multistep-carcinogenesis (from Surh et al. with modifications [69]).

A distinct class of chemopreventive agents including curcumin and resveratrol (Fig. 2) belong to both categories as they present multiple mechanisms of action.

For this review, we summarize one of the best characterized chemopreventive agents, curcumin or diferuloylmethane extracted from the root of *Curcuma longa L.* (Fig. 3) which presents strong

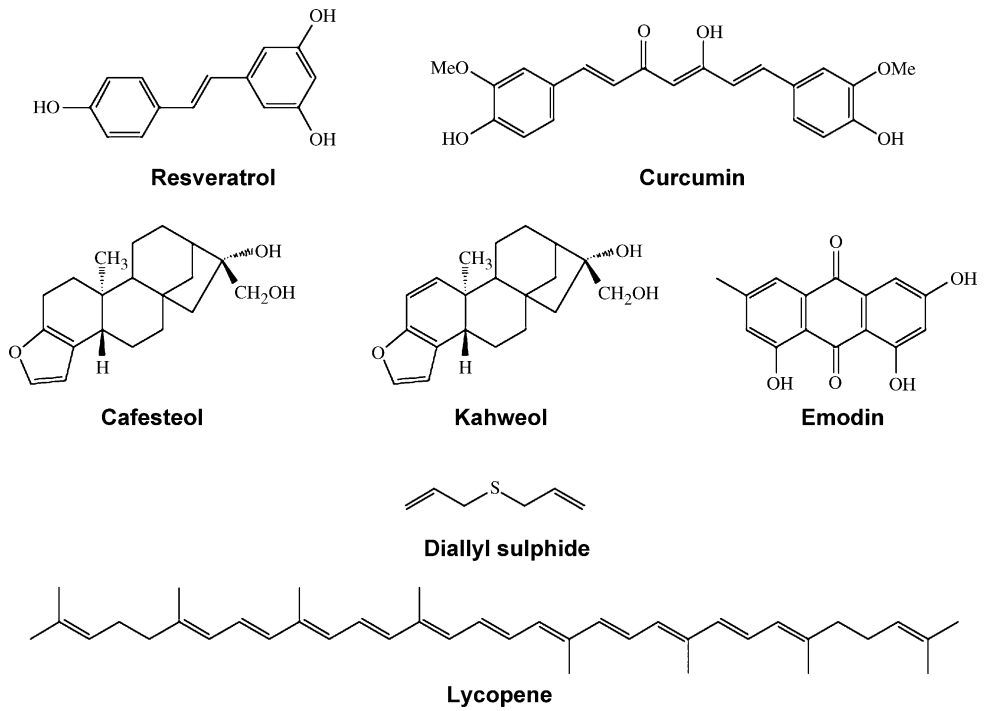

Fig. 2. Molecular structure of selected chemopreventive agents.

Fig. 3. *Curcuma longa L.* (© 1995–2004 Missouri Botanical Garden, http://ridgwaydb.mobot.org/mobot/rarebooks).

anti-oxidative, anti-inflammatory and anti-septic properties [5] and is widely used in Indian medicine and culinary traditions. However, recent data give additional evidence that curcumin could also serve in cancer therapy as a drug or as an adjuvant to traditional chemotherapy. This review will focus on both chemopreventive and chemotherapeutic effects of curcumin.

2. Anti-carcinogenic activities of curcumin

Numerous research teams provided evidence that curcumin contributes to the inhibition of tumour formation and promotion as cancer initiation, promotion or progression of tumours is decreased or blocked by this compound. Azuine et al. [6,7] described curcumin as an inhibitor of tumour

formation and promotion induced by benz(a)pyren, 7,12-dimethylbenz(a)anthracen or phorbol esters, while Ikezaki et al. [8] demonstrated that curcumin inhibits cancer development in rat stomach initiated by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG). In the same way, bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione, a bisdemethoxycurcumin analog (BDMC-A), blocks the formation of colon adenocarcinoma in rats [9]. Although curcumin does not decrease the copper-induced liver or kidney tumour incidence in Long-Evans Cinnamon (LEC) rats, an inbred mutant strain which accumulates copper due to an aberrant copper-transporting ATPase gene, it reduces overall cancer formation as well as formation of metastasis [10]. Furthermore, curcumin was described as a good anti-angiogenesis agent [11], explaining its chemopreventive effect at the level of tumour promotion. This phenomenon could be explained by vascular endothelial growth factor (VEGF) and angiopoietin 1 and 2 inhibition in EAT cells, by VEGF and angiopoietin 1 inhibition in NIH 3T3 cells and by inhibition of the tyrosine kinase Flk-1/KDR (VEGF receptor-2) in HUVEC cells [12]. Concerning clinical trials, curcumin was given to patients with early stages of cancer up to 12 g/day [13]. This treatment did not present cytotoxicity up to 8 g/day, however beyond 8 g/day, the bulky volume of the drug became unacceptable to patients. Anti-cancer effect of curcumin seems to be potentialized in the presence of oestrogen in breast cancer cells and it inhibits genes which are under the influence of the oestrogen receptor [14]. Curcumin also displays an inhibiting effect on human telomerase reverse transcriptase (hTERT) expression, reducing telomerase activity in MCF-7 cells [15]. Moreover, it allows sensitising ovarian cancer cells to cisplatin, enhancing chemotherapeutic treatment [16].

3. Contribution of curcumin to the induction of apoptotic mechanisms

The ability of curcumin to induce apoptosis in cancer cells without cytotoxic effects on healthy cells contributes to the understanding of the anti-cancer potential of curcumin. This spice is described to efficiently induce apoptosis in various cell lines including HL-60, K562, MCF-7 and HeLa [17]. Curcumin also leads to apoptosis in scleroderma lung fibroblasts (SLF) without affecting normal lung fibroblasts (NLF) [18]. This effect seems to be due to the weak level of protein kinase (PK) Cε in SLF, generating low levels of glutathione *S*-transferase (GST) P1-1.

Woo et al. [19] suggested that the induction of Caki (human kidney carcinoma cells) programmed cell death is activated by Akt dephosphorylation (Fig. 4a), Bcl-2, Bcl-XL and inhibitor of apoptosis (IAP) protein inhibition, as well as cytochrome *c* release and caspase 3 activation (Fig. 4b). These findings confirm results by Bush et al. [20], Anto et al. [21] and Pan et al. [22] studying caspase 3 activation in melanoma and HL-60 cells. Bush et al. [20] described that curcumin induces caspases 8 and 9, although p53 remains unchanged. Nevertheless, the death receptor pathway is activated through Fas in a Fas-Ligand independent way. Anto et al. [21] confirmed the role of Bcl-2 and Bcl-XL inhibition by preventing curcumin-induced apoptosis after over expressing these two key proteins (Fig. 4b). In U937 monocytic lymphoma cells Bcl-XL and IAP inhibition, cytochrome *c* release and caspase 3 activation were described (Fig. 4b) [23]. On the opposite, apoptosis in Jurkat cells is described to be caspase 3 independent, its activation being blocked by an increase of glutathione (GSH) levels [24–26]. Caspase activation by curcumin was described to be blocked by heat shock protein (HSP), which do not influence cytochrome *c* release [27]. However, Jana et al. [28] demonstrated that curcumin inhibits proteasome activity in mice, potentially leading to induction of apoptosis through caspase 9 activation.

Unfortunately, in selected pathologies, curcumin is able to inhibit chemotherapeutic effects by reducing camptothecin-, mechlorethamine- or doxorubicin-induced apoptosis in breast cancer cells [29]. Curcumin exhibited anti-oxidant properties and inhibited both JNK activation and mitochondrial release of cytochrome *c* in a concentration-dependent manner. Nevertheless, association of curcumin with other anti-cancer drugs should be carefully evaluated in breast cancer. Even a limitation of exposure of patients to curcumin-containing foods should be considered.

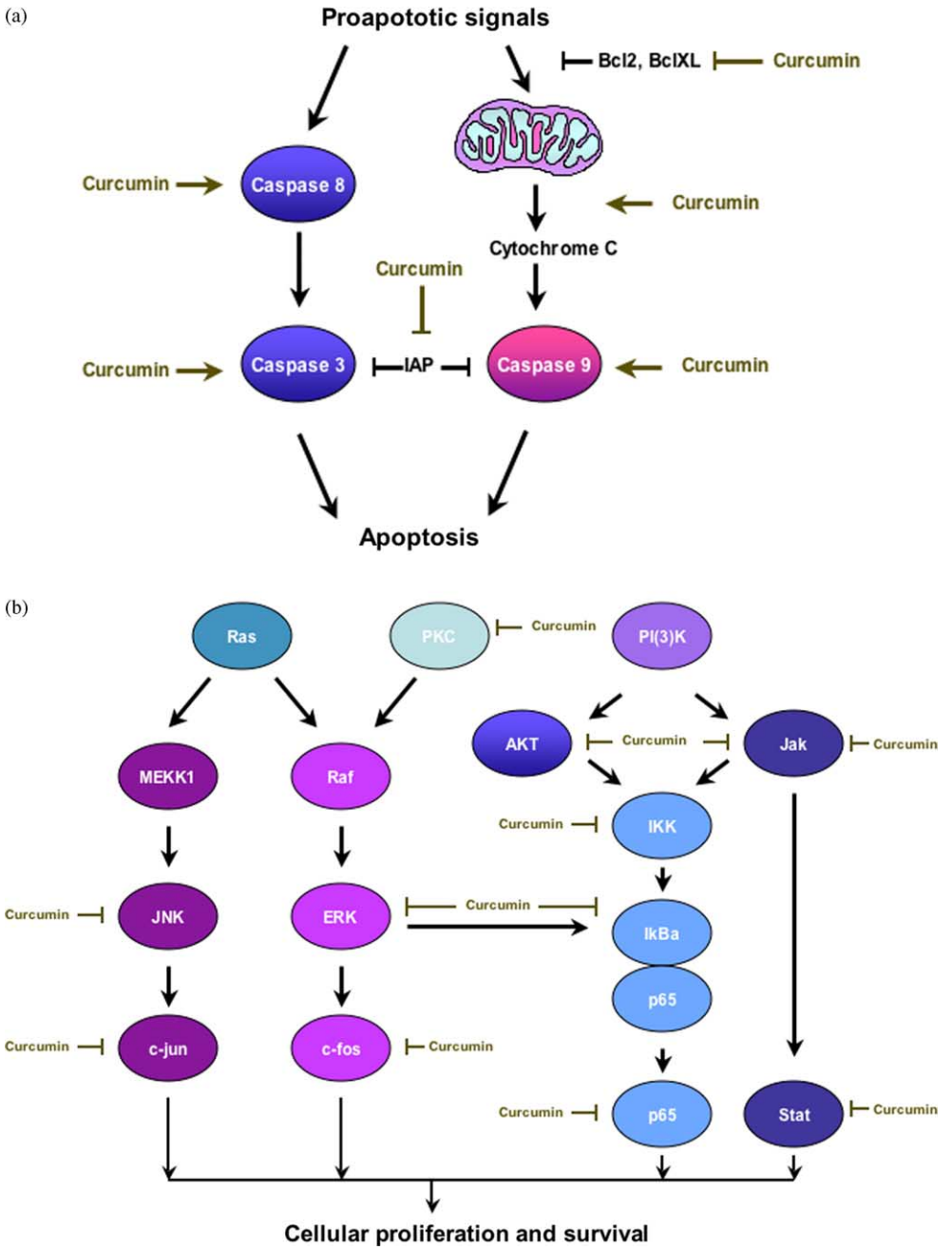

Fig. 4. Signal transduction pathways affected by curcumin treatment leading (a) to controlled cell death or (b) to cellular proliferation and survival.

4. Anti-inflammatory effects of curcumin

It was published that curcumin inhibits cyclo-oxygenase 2 (COX-2) as well as lipoxygenase (LOX), two enzymes involved in inflammation [30]. Indeed, cytokine-induced COX-2 transforms arachidonic acid in prostaglandins during acute inflammatory episodes. COX2 is also the prevalent isoform during chronic

inflammations. Lipoxygenase transforms arachidonic acid in leukotrienes, which take part in leukocytes recruiting and play a role in inflammation [31].

Moreover, curcumin protects keratinocytes and fibroblasts against H_2O_2-induced damages [32] and allows reduction of oxidative and inflammatory stress in Alzheimer patients [33]. Pancreatitis improves after curcumin treatment, which blocks key inflammatory signals [34]. However, by verifying the effect of curcumin in galactose-induced cataract, Suryanarayana et al. [35] discovered that small doses of curcumin (0.01%) could increase oxidative stress in hyperglycaemic rats.

5. Inhibition of nuclear factor kappa B and activating protein-1 transcription factors

It was previously published that curcumin inhibits the activation of the two major transcription factors nuclear factor kappa B (NF-κB) and activating protein (AP)-1. Our group described this effect in K562 leukemia cells in which curcumin strongly inhibits tumor necrosis factor (TNF) α-induced NF-κB and TPA-induced AP-1 binding to the corresponding target sequences on GSTP1-1 gene promoter or consensus binding sites [36]. Bharti et al. [37] discovered that IκB kinase (IKK) complex inhibition blocks both IκBα phosphorylation as well as NF-κB p65 translocation and thus leads to NF-κB inhibition. Several teams confirmed these results and published that curcumin inhibits interleukin (IL) 1α-, TNFα-, TPA-, lipopolysaccharide (LPS)- and thrombin-induced NF-κB activation. This inhibiting effect should be considered to improve chemotherapeutic treatment as most anticancer drugs, including doxorubicin induce NF-κB leading to the development of drug resistance [38–43]. Cigarette smoke, which contains numerous carcinogenic agents such as superoxide and hydroxyl radicals, H_2O_2 and benz(a)pyren, activates NF-κB, blocks apoptosis and induces proliferation and carcinogenesis. Curcumin abolishes the induction of NF-κB binding to the DNA, blocks IKK activation, IκBα phosphorylation and degradation as well as NF-κB p65 translocation [44]. NF-κB inhibition by curcumin is certainly an interesting strategy against diseases such as the pathogenesis of alcoholic liver disease, in which NF-κB is activated [45].

As for AP-1, Chen and Tan [46] demonstrated that curcumin inhibits the signal transduction pathway leading to JNK activation at mitogen-activated protein kinase kinase kinase (MAPKKK). Furthermore, the signaling pathway leading to MAP kinase p38 activation is attenuated by curcumin in inflammatory bowel disease cells [47], whereas Akt kinase is completely inhibited in prostate cancer cells [48]. Curcumin also inhibits c-Fos transcription factor activation by inhibition of extracellular-signal-regulated kinase (ERK) and JNK [49].

Protein kinase C is involved in redox modulation in the cell: oxidants activate PKC by interaction with the regulatory domain and thus generating a cellular signal for cellular growth and tumour promotion, while anti-oxidants inhibit the catalytic domain of PKC [50]. Curcumin also inhibits TPA-induced c-Jun and c-Fos activation by acting at the PKC level in a non-competitive way [51,52]. Furthermore, TPA-induced PKC is abolished by curcumin in NIH 3T3 mouse fibroblast cells [53]. Interestingly, Dickinson et al. [54] demonstrated that curcumin modifies AP-1 dimer composition. Indeed, JunD and c-Jun play key roles during curcumin treatment, modifying glutamate-cystein ligase gene expression and other phase II enzyme genes in HBE1 cells.

Curcumin was described to act on the Janus Kinase-Signal Transducer and Activator (JAK/STAT) pathway. Curcumin inhibits IL-12 activation by blocking JAK 2, tyrosine kinase 2, STAT3 and STAT4, in experimental allergic encephalomyelitis, a model of multiple sclerosis [55]. However, curcumin is an activator of heme-oxygenase (HO)-1 through the activation of Nrf2/anti-oxidant response element (ARE) pathway in kidney epithelium cells [56]. In kidney cells, inhibition of IkBα phosphorylation decreases HO-1 induction by curcumin thus involving the NF-κB pathway [57]. Curcumin also directly acts on the amount of free radical within the cell by decreasing superoxide radical levels [58].

6. Effect on detoxification enzyme expression mechanisms

Cytochrome P450 (CYP) are phase I enzymes involved in activation of carcinogens whose inhibition

adds a degree of cellular protection against cancer. It was previously published that curcumin inhibits alkylation reaction of ethoxyresorufin, methoxyresorufin and pentoxyresorufin catalysed by CYP 1A1, 1A2 and 2B1 in rat liver [59]. Similarly, aflatoxine-DNA adduct formation, catalysed by the CYP system, is inhibited by curcumin [60]. In DMBA-treated MCF7 cells, CYP activity is dramatically reduced by curcumin, which binds directly to the aryl hydrocarbon receptor (AhR) and thus prevents binding of this transcription factor to the xenobiotic response element (XRE) present on the CYP gene promoter [61]. Interestingly, Rinaldi et al. [62] illustrated that curcumin activates the AhR while inhibiting carcinogen activation induced by CYP 1A1 in both oral SCC cells and intact oral mucosa. These authors suggest that the use of curcumin as an oral cavity chemopreventive agent could have a clinical impact via its ability to inhibit carcinogen bioactivation.

Evidence was also presented that curcumin induces the activity of phase II drug metabolizing enzymes in male mice, particularly GST and quinone reductase in liver and kidney [63]. However, this effect seems to be concentration-dependent and, if curcumin activates GST at low doses, high concentrations inhibit GST activity in rat [64]. In the same way, van Iersel et al. [65] documented that curcumin is a strong GST inhibitor in human melanoma cells in which GSTP1-1 is the major isoform. Our group confirms those results by providing evidence that curcumin significantly reduces GSTP1-1 expression in K562 and Jurkat leukemia cells [36,66] by inhibiting NF-κB and AP-1 signalling pathways. In parallel, curcumin inhibits GST activity as well as CYP 1A1/1A2 in cells treated with different agents such as phenobarbital, β-naphtoflavone and pyrasol [67] whereas in rat, curcumin allows the restoration of normal levels of GSTP in hepatic cells [68].

7. Conclusions

The available experimental evidence suggests that it is worth testing curcumin as a cancer therapeutic agent. All published observations indicate that curcumin leads to a strong modification of cell signalling pathways including a reduction NF-κB and AP-1 transcription factors. In conclusion, cell-type specific effects of curcumin are highly significant in selected pathologies and future research will allow a better understanding of pathways targeted by curcumin as well as its chemical derivatives.

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